Diagnostic Characteristics of Clozapine-Induced Myocarditis Identified by an Analysis of 38 Cases and 47 Controls

Kathlyn J. Ronaldson, MSc, DPhil; Andrew J. Taylor, MBBS, FRACP, PhD; Paul B. Fitzgerald, MBBS, MPM, FRANZCP, PhD; Duncan J. Topliss, MBBS, FRACP, MD, FACE; Maros Elsik, BSc (Med), MBBS, FRACP; and John J. McNeil, MBBS, FRACP, MSc, PhD, FAFPHM

Objective: To analyze cases of clozapine-induced myocarditis for clinical and diagnostic trends.

Method: A case definition was developed by a multidisciplinary group using reports of myocarditis with clozapine submitted to the Australian Therapeutic Goods Administration. The definition uses for diagnosis either histology or the combination of new signs of cardiac dysfunction combined with a cardiac-specific diagnostic parameter occurring within 45 days of starting clozapine. Potential cases of clozapine-related myocarditis occurring between January 1993 and September 2008 and a comparative group of long-term clozapine users were documented from the patients’ medical records.

Results: Thirty-eight of 59 reviewed cases met the case definition. Three patients died, and the diagnosis for these was confirmed on cardiac histology. Nearly all of the remaining patients had persistent tachycardia and elevated troponin level. The time to onset was 14–22 days in all except 2 patients. Of the patients who survived, 66% (23 cases) had eosinophilia occurring 0–7 days (mean, 4.0) after the peak in troponin. C-reactive protein (CRP) level was elevated to above 100 mg/L (952 nmol/L) in 79% (23 cases), and some had elevated levels of CRP when troponin level was still normal. None of the control group (47 patients) met the case definition.

Conclusions: Eosinophil counts should not be relied on for diagnosis of clozapine-related myocarditis, but elevated CRP may be an early indicator of developing myocarditis. Patients starting clozapine should be actively monitored for myocarditis during the first 4 weeks, with extra care taken during week 3.
Compliance With the Case Definition

In 30 cases, the cardiac specific diagnostic parameters were basal lung crepitations and/or peripheral edema in 3 cases. Of documented sustained tachycardia in 32 cases and by clinical criteria for myocarditis were met by the presence of histologic evidence of myocarditis at autopsy. For the remaining 35 cases, the case reports.

Therapeutic Goods Administration for access to original a Deed of Confidentiality and Conflict of Interest with the National Coroners’ Information Service database and the Victorian Institute of Forensic Medicine for access to consent. In addition, an Access Agreement was signed with approvals covered access to medical records without patient consent. In addition, an Access Agreement was signed with the Victorian Institute of Forensic Medicine for access to the National Coroners’ Information Service database and a Deed of Confidentiality and Conflict of Interest with the Therapeutic Goods Administration for access to original case reports.

RESULTS

Compliance With the Case Definition

Of 59 cases reviewed, 38 met the case definition. Three cases were fatal and for these the diagnosis was made by cardiac histology at autopsy. For the remaining 35 cases, the clinical criteria for myocarditis were met by the presence of documented sustained tachycardia in 32 cases and by basal lung crepitations and/or peripheral edema in 3 cases. In 30 cases, the cardiac specific diagnostic parameters were satisfied by at least 1 troponin I or T measurement greater than or equal to twice the upper limit of normal. In each of these cases, the patient had a documented normal troponin level at baseline. The 5 cases without raised troponin level had diagnostic confirmation by evidence of left ventricular impairment by echocardiography (4 cases) or gated blood pool scan (1 case). In 1 patient, the diagnosis of myocarditis was confirmed by magnetic resonance imaging.

Twenty-one potential cases were excluded for the following reasons: the time to onset was more than 45 days (3 cases), other disease states may have caused confounding (4 cases), insufficient data were available to make an assessment (2 cases), or the clinical and diagnostic criteria were not met by the data (12 cases).

Characteristics of the Cases

The characteristics of the confirmed cases are presented in Table 2 and the diagnostic features in Table 3.
Echocardiography (29 cases) or gated blood pool scan (1 case) was performed 0–5 days after stopping clozapine. Of these 30 patients, 22 had left ventricular impairment with ejection fraction ranging from the lower limit of normal to 30%. All except 2 of 18 cases with baseline echocardiography had deterioration in cardiac function from baseline. Two patients, 1 of whom died, had no symptoms associated with myocarditis. Eighteen patients had persistent fever for up to 6 days before troponin was found to be elevated or other diagnostic measures indicated myocarditis. Several of these had normal troponin after onset of fever. Other symptoms associated with myocarditis were sore throat, vomiting, diarrhea, headache, dyspnea, and neck pain. The variety in clinical presentation is illustrated by the 5 case histories in Table 4.

Peripheral eosinophilia developed in 66% of the nonfatal cases (see Table 3), but a notable feature was a delay in the increase in eosinophil count, with the peak occurring from 0 to 7 days (mean ± SD, 4.0 ± 2.2) after the maximum observed troponin I or T value. Because of this delay, none of the fatal cases developed eosinophilia. In 5 instances, C-reactive protein (CRP) level was above 100 mg/L (ULN 0.5), CRP 224 mg/L, creatine kinase 587 U/L and left ventricular ejection fraction 20%–39%. Pulmonary embolism, bacterial infection, and neuroleptic malignant syndrome were investigated and excluded.

Case Recovery

Except for the fatal cases and 1 who appeared well throughout, all identified cases of clozapine-associated myocarditis experienced improvement in constitutional symptoms following withdrawal of clozapine. Recovery was reflected by return of heart rate to less than 100 beats per minute (29 cases) and a fall in troponin level to normal (25 cases) or an incomplete reduction (3 cases). All except 1 of the 35 nonfatal cases had documented return of either heart rate or troponin levels to within the normal range. The exception had a fall in troponin I level to half of the maximum with no further determinations.

Follow-up cardiac imaging more than 5 days after clozapine cessation was available for 17 cases: 12 showed normal cardiac function, 4 showed improvement, and 1 was unchanged. The patient without improvement 7 days after stopping clozapine nevertheless had normalization of heart rate and troponin level.

---

### Table 2. Characteristics of the 38 Cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Range</th>
<th>Outliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>27</td>
<td>11–73</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>0–17</td>
<td>20</td>
</tr>
<tr>
<td>Age, y</td>
<td>38 ± 13</td>
<td>22–73</td>
<td>22</td>
</tr>
<tr>
<td>Duration of clozapine, d</td>
<td>17.5 ± 2.3</td>
<td>14–22</td>
<td>26 and 33</td>
</tr>
<tr>
<td>Dose at onset, mg/d</td>
<td>232 ± 69</td>
<td>100–400</td>
<td>50 and 750</td>
</tr>
</tbody>
</table>

---

### Table 3. Diagnostic Features of the 38 Cases of Myocarditis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Present</th>
<th>Absent</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia (heart rate &gt; 100 bpm)*</td>
<td>34</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate ≥ 120 bpm</td>
<td>30</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Fever (&gt; 37°C)</td>
<td>35</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Chest pain</td>
<td>22</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Troponin I/T level ≥ 2ULN</td>
<td>31</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Left ventricular impairment by</td>
<td>22</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>cardiac imaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>29</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>T-wave abnormalities</td>
<td>27</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>ST-elevation/depression</td>
<td>14</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>CK-MB level &gt; ULN</td>
<td>2</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>Creatine kinase level &gt; ULN</td>
<td>11</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>Eosinophil count &gt; ULN</td>
<td>23</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Eosinophil count ≤ 0.1 × 10⁹/L</td>
<td>6</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>C-reactive protein level &gt; 100 mg/L</td>
<td>23</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>ESR &gt; 50 mm/hr</td>
<td>7</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>White blood cell count &gt; ULN</td>
<td>22</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Neutrophil count &gt; ULN</td>
<td>27</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Monocyte count &gt; ULN</td>
<td>12</td>
<td>26</td>
<td>0</td>
</tr>
</tbody>
</table>

---

### Case Vignettes

Case 1: The heart rate of a patient rose to 133 (baseline 100) bpm after 16 days of clozapine. Troponin I level was not raised above normal, but echocardiography showed deterioration in ejection fraction from a baseline of >59% to 40–59%. CRP rose to a maximum of 190 mg/L.

Case 2: A patient died while asleep after taking clozapine (current dose 750 mg/d) for 33 days. Hypersensitivity myocarditis was diagnosed by histology at autopsy. Although the patient had been hospitalized from the time of starting clozapine, there had been no indication of physical illness. Weekly blood tests were due the following day.

Case 3: A patient developing a fever with tachycardia of 120 bpm after 17 days of clozapine had normal troponin the following day, although CRP was elevated to 113 mg/L. Another normal troponin level was followed by an elevated value on day 21. Myocarditis was further confirmed by echocardiographic evidence of new left ventricular dysfunction.

Case 4: After taking clozapine for 20 days, a patient had basal crepitations but only brief periods with a heart rate of 100 beats/min or more. Troponin I level was 5.6 µg/L (ULN 0.5), CRP 224 mg/L, creatine kinase 587 U/L and left ventricular ejection fraction 20%–39%. Pulmonary embolism, bacterial infection, and neuroleptic malignant syndrome were investigated and excluded.

Case 5: A patient developed a sore throat, stiff joints, neck pain, fever, tachycardia, and chest pain on clozapine day 15. Despite the indications of neuroleptic malignant syndrome, creatine kinase was not elevated; maximum recorded was 61 U/L. Further, no infectious cause was identified. Troponin was 0.11 µg/L (ULN 0.03), CRP 475 mg/L; and left ventricular ejection fraction, 30%–35%.

---

**Abbreviations:** bpm = beats per minute, CK-MB = creatine kinase-MB, ECG = electrocardiogram, ESR = erythrocyte sedimentation rate, ULN = upper limit of normal.
Comparative Group

Forty-seven of 69 patients reviewed met the criteria for the comparative group. These 47 patients were aged 19–73 years (mean ± SD, 37 ± 13), and 32 were male and 15 female. Table 5 presents the results of investigations relevant to the exclusion or diagnosis of myocarditis in this group, and Figure 1 compares the rates of 5 features for cases and controls.

The odds ratio for eosinophilia 14–28 days after starting clozapine for cases with myocarditis versus the comparative group was 3.29 (95% CI, 1.21–9.02; \( P = .009 \)). The sensitivity of eosinophilia for a diagnosis of myocarditis was 61% and specificity, 68%. Eight control patients had both eosinophilia and tachycardia.

DISCUSSION

Study Strengths

A number of factors of the Australian context have allowed us to obtain detailed documentation of the initiation of clozapine for both the cases and the controls and for the clinical presentation of myocarditis in the patients in whom it developed. Clozapine is typically initiated in a hospital, with close monitoring of the patient’s vital signs, minor side effects, as well as hematologic and cardiac parameters. Much of the literature about clozapine-related myocarditis has been generated from Australia, and it is well recognized in this country. The well supported adverse reaction monitoring system has led to reports being accumulated from across Australia and has in turn generated added awareness of this serious adverse effect.

This is the first study to systematically document multiple cases of clozapine-induced myocarditis from patient medical records. Clozapine initiation commonly causes a variety of minor signs and symptoms, some of which, including tachycardia, eosinophilia, and fever, may confound the diagnosis of myocarditis. We have established a case definition that distinguishes between myocarditis and these other benign conditions, as demonstrated by none of the comparative group meeting the case definition. The suitability of the case definition is further supported by the rapid recovery of the surviving cases in this group following withdrawal of clozapine. From this foundation, we have been able to examine cases of myocarditis and identify clinical characteristics of myocarditis that can inform monitoring and early diagnosis in the future.

Time to Onset

This analysis has used the duration of clozapine as a surrogate for the time to onset, and the duration of clozapine in 36 of 38 cases was 14–22 days. The possibility of bias with respect to time to onset of myocarditis in this study should not be overlooked. All except 1 case were identified to the researchers because they were recognized by a treating clinician in the first instance. Clinicians are more likely to recognize cases occurring earlier rather than later in the course of clozapine because of a heightened level of alertness to adverse reactions in the early stages of a new treatment, because of the cardiac monitoring protocol with checks at days 7 and 14, and because, although most start clozapine in hospital, few are hospitalized for more than 3 weeks after initiation. In published cases, the time to onset is typically 7–35 days. It is possible that time to onset is a function of rate of dose titration, but this is yet to be investigated.

Heart Rate as a Diagnostic Characteristic

It should be noted that tachycardia (heart rate > 100 beats/min) as a diagnostic feature of cases was required to persist for at least 24 hours. However, when tachycardia was recorded in a control patient, data on persistence were usually not available and were not documented. Hence, the
comparison of frequency of heart rate of more than 100 beats per minute for cases and controls places a stricter requirement on cases (Figure 1). For the comparison of frequency of heart rate of 120 or more beats per minute, persistence was not a criterion for either group.

With regard to the validity of persistence of tachycardia as a diagnostic feature, it was supported by conjunction in time with symptoms of illness and the presence of cardiac-specific diagnostic measures, followed by resolution of these, including tachycardia, on withdrawal of clozapine.

**Eosinophil Count, C-Reactive Protein Level, and Fever**

A recently published review advises determining eosinophil count as a means to diagnosis of clozapine-related myocarditis. In the present series, 66% of the nonfatal cases experienced eosinophilia, and, surprisingly, the elevation in eosinophil count was delayed for as long as 7 days after the peak in troponin I/T levels. Checking for eosinophilia would not assist in the early diagnosis of myocarditis and, most importantly, would not prevent fatalities. Furthermore, overreliance on peripheral eosinophil count could result in clozapine withdrawal in a patient without myocarditis, as indicated by the 32% incidence of eosinophilia in the comparative group.

In contrast, there are indications that CRP may be the first measurable parameter to herald the onset of a disease process. While it is a nonspecific inflammatory marker, elevations above 50 mg/L would be a reason to monitor the health of the patient more closely, particularly by daily electrocardiography (ECG) and troponin determinations. Similar monitoring advice could be associated with the development of fever, and a normal troponin determination after the development of fever does not mean that myocarditis has been excluded; rather, the fever may be part of an evolving myocarditis prodrome.

**Limitations**

A limitation of this case analysis is that it was constrained by the investigations that the treating clinician of each individual patient chose to conduct. For instance, it was not possible to fully explore the value of CRP as an early indicator of myocarditis. Similarly, daily eosinophil counts would have assisted in the characterization of the observed delay in the development of eosinophilia.

**Other Countries**

Countries other than Australia, and perhaps New Zealand, have reported very few cases of myocarditis considering clozapine usage. Various causes have been postulated including genetic differences and high ozone in the breathed atmosphere of the southern hemisphere. A plausible reason, however, is that cases have been missed in other countries. The presentation of myocarditis is nonspecific. It may resemble influenza or there may be no symptoms. Added to this are patient factors, such as psychiatric illness, which typically is poorly controlled at the time of clozapine initiation, making it difficult for patients to communicate symptoms they feel. Without a preceding high level of awareness of the association and hence active investigation for myocarditis, it very likely will be missed, especially if clozapine is initiated without the clinical scrutiny inherent in hospitalization.

A recent analysis of data from a health maintenance organization in the United States found a higher rate of mortality from sudden cardiac death in community patients treated with clozapine than with any other antipsychotic. The study included no data on time to onset, but it is at least feasible that myocarditis may have contributed to the excess of deaths.

**Monitoring**

Not all centers internationally routinely initiate clozapine with the patient hospitalized, but weekly blood count monitoring is mandatory in several countries (Australia, Canada, New Zealand, United Kingdom, and United States) during the first 18 weeks. Diagnosis of myocarditis would be improved if the collected blood were also used to check cardiac parameters (troponin I or T) and CRP and an ECG taken at baseline and at 7, 14, 21 and 28 days. Whether the patient is treated in the community or as an inpatient, he or she should be seen by a physician and examined for signs and symptoms of illness at each of these intervals. Although chest pain was present in only 58% of cases in this study, it may be a useful indicator. Those with elevated CRP or indications of illness not conclusively diagnosed as having another cause should be closely monitored over the next few days. Further, patients and their carers should also be advised to report any illness, between the dates of routine tests, to a physician during this critical 4-week period. If troponin level is elevated or a new ECG abnormality is detected, clozapine should be discontinued pending further investigation.

**CONCLUSION**

In the absence of a gold standard for the diagnosis of clozapine-associated myocarditis, our case definition is a simple algorithm that can assist clinicians to identify clozapine-related myocarditis while excluding those with benign rises in eosinophil counts and heart rate. This analysis of 38 cases found that the typical time to onset of clozapine-related myocarditis is 14–22 days after starting clozapine and that eosinophil counts are a poor tool for diagnosis. Patients starting clozapine should be actively monitored for myocarditis during the first 4 weeks, with extra care taken during week 3. Rises in CRP level and development of fever may be early indicators of myocarditis and daily ECG and troponin measurements in the presence of fever or following a CRP level of more than 50 mg/L may be diagnostically useful.
Drug name: clozapine (FazaClo, Clozaril, and others).

Author affiliations: Department of Epidemiology and Preventive Medicine, Monash University (Drs Ronaldson, McNeil, and Elsk); and the Heart Centre (Dr Taylor), Monash Alfred Psychiatric Research Centre (Dr Fitzgerald), and Department of Endocrinology and Diabetes (Dr Topliss) the Alfred Hospital, Melbourne, Victoria, Australia.

Potential conflicts of interest: None reported.

Funding/support: A salary was paid to Dr Ronaldson in 2006 and 2007 from a grant from the Australian National Health and Medical Research Council.

Acknowledgments: The authors are grateful for the assistance of individuals at each of the following health services: from Victoria, Barwon Health (Dr T. Callalry, Mr W. Kuliris, Ms D. Grapsas), Bayside Health (Ms K. Hirth, Ms C. Forrester, Ms A. Given, Ms L. Scarff, Ms L. Hughes, Ms A. La Trobe, Ms J. Giuliani, Mrs D. Elliott), Bendigo Health (Dr P. Chopra, Ms S. Maynard), Eastern Health (Assoc Prof P. Katz, Ms J. Jolly, Ms A. McClaren), North West Mental Health (Dr K. Morton, Ms Gisella Campanelli, Ms A. Hammod, Ms A. Gilchrist, Mr A. Cox, Ms H. Manos), Peninsula Health (Assoc Prof R. Newton, Mr G. Dobson), Southern Health (Dr S. Dammoradan, Ms A-M Foster, Ms L. Rouda, Mr D. Graham, Mr A. Koca), Thomas Embling Hospital (Dr A. Brennan), and Werribee Mercy Mental Health Service (Dr S. Ivespersen, Assoc Prof D. Stevenson, Mrs K. Hodge, Ms F. Gleeson, Ms K. Gray); and from New South Wales, Northern Sydney Central Coast Health (Dr M. Paton, Dr L. Newton, Mr J. Glen, Mr J. Bajuk, Ms A. Steele, Mrs P. Wheeler).

REFERENCES


